IN THE DRAWINGS:

Subject to the approval of the Examiner, please replace the originally filed drawings in this application with new drawings, 70 pages, Figures 1 through 49, attached hereto.

REMARKS

Formal Matters

Claims 1-2 and 4-24 are now pending in the application; however, only claims 2, 4-6, 9-10, 13, and 24 are currently under examination. The remaining claims have been withdrawn from consideration. Applicants thank the Examiner for withdrawing many of the formalistic objections to the claims, as well as many indefiniteness rejections.

The Examiner has maintained his objection to the specification for failing to comply with 37 C.F.R. § 1.821(d). Applicants submit new formal drawings with this application and ask that the drawings be entered into the application.

Objection to Improper Claim Dependency

The Examiner has objected to claims 3-6, 9-10, and 13 as dependent on non-elected inventions. The Examiner particularly objects to claim 3 and 9 as dependent on non-elected inventions (P40/PHAII and P30/PHAPI).

Applicants do not believe that the Examiner's objection is proper. While Applicants have elected the species of P95/nucleolin, Applicants have retained the right to have the Examiner consider claims to additional species which are written in dependent form or otherwise include all of the limitations of the generic claim 2. *See*

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M.P.E.P. § 809.02(a). Thus, Applicants request that the Examiner withdraw this objection.

Enablement Rejection

The Examiner has rejected claim 13 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. The Examiner believes that claim 13, which the Examiner alleges is directed to the prevention and/or treatment of HIV infection is not enabled. The Examiner points to the fact that the specification only provides *in vitro* not *in vivo* data regarding the claimed composition. The Examiner states that the *in vitro* tests are not correlated with *in vivo* results. Additionally, the Examiner states that the specification does not discuss which peptides should be used, how they should be administered, etc.

The Examiner, thus, seems concerned that the application has not enabled a method of treating or preventing HIV infection. In responding to this rejection, Applicants wish to point out that claim 13 recites a composition, not a method of treatment. Applicants have amended claim 13 to remove the terms "therapeutic" and "pharmaceutically effective amount" to more particularly point out and definitely claim the invention, which is a composition, not a method of treatment. Merely claiming a composition that is combined with another anti-HIV molecule does not require a showing that such a treatment would be effective against HIV. Thus, Applicants believe that the rejection should be withdrawn as the application does not claim a method for treating or preventing HIV infection.

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Nevertheless, Applicants wish to provide evidence that the *in vitro* tests used in the specification to evaluate the claimed inhibitor molecules are predictive of *in vivo* results. These tests were also used by the Applicants to evaluate the TASP peptide. The corresponding *in vitro* tests of the TASP peptide using the CEM cell model are provided in the *Callebaut* reference cited by the Examiner. *Callebaut*, at 183, "Assay of HIV entry;" 184, "Assay of the inhibitory effect of peptide-TASP constructs on HIV infection." Results showing the inhibition of HIV infection are shown in Figures 2 and 4. *Callebaut*, at 185, Figure 2; 187, Figure 4.

The CEM cell model of HIV infection was validated as predictive of *in vivo* results. The TASP peptide was shown, in a rat study, to be preferentially taken up by lymphoid organs (the known site of HIV pathogenesis). *Krust et al.*, PNAS 98:14090-14095, at abstract and 14094, right column through 14095, left column (2001). This preferential uptake is consistent with activity in tissues where HIV replicates. *Id.* The TASP peptide was also found to be highly stable in donated human serum, retaining more than 80% of its activity and indicating that it would be circulated *in vivo* and would be able to function in human serum. *Callebaut et al.*, J. Biol. Chem. 272:7159-7166, at 7163, Table II (1997).

Additional *in vitro* experiments also provided results similar to the CEM cell model, illustrating that it is an acceptable model for testing inhibitors of HIV infection. The TASP peptide was also found to inhibit HIV infection in primary macrophage cultures. *Seddiki et al.*, The V3 Loop-Mimicking Pseudopeptide 5[Kφ(CH_2N)PR]-TASP Inhibits HIV Infection in Primary Macrophage Cultures, AIDS Research and Human

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Retroviruses 15(4):381-390, at 386, discussion (1999). Additionally, it is shown to inhibit attachment of T lymphocyte- and macrophage-tropic HIV to permissive cells. *Nisole et al.,* The HB-19 Pseudopeptide 5[Kφ(CH_2N)PR]-TASP Inhibits Attachment of T Lymphocyte- and Macrophage-Tropic HIV to Permissive Cells, AIDS Research and Human Retroviruses 16(3):237-249, at 242 (2000).

The *in vitro* tests in the current application also use the CEM cell model of HIV infection to test the claimed inhibitors of the present invention. Specification, at 93. The claimed inhibitors were shown to inhibit HIV-1 infection in the *in vitro* system. *Id.* at 121-122 (Example 15). Applicants believe, based on the showings above, that the CEM cell model of HIV infection is predictive of *in vivo* results.

Applicants maintain that this showing is not necessary, as the present claims are only directed to compositions, not methods of treatment, and Applicants believe that the present invention is enabled. Applicants request that the Examiner withdraw the rejection of claim 13.

Definiteness Rejection

The Examiner has rejected claims 2-6, 9-10, and 13 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner, however, did not set forth a specific definiteness rejection for claim 13. Applicant request that the rejection to claim 13 be articulated or withdrawn

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Claim 2

The Examiner rejected claim 2 as indefinite for using the phrases "peptidic or non-peptidic inhibitor molecule," "inhibitor is not nuclear nucleolin", and "able to." The Examiner was not convinced by the arguments that the inhibitor can be either a peptide or a non-peptide, accompanied by the definition of a peptide.

Applicants have deleted the phrase "peptidic or non-peptidic" in order to facilitate prosecution. Applicants intend to claim all inhibitors that inhibit and/or prevent the interaction between the HIV receptor and the gp120 envelope glycoprotein. As the inhibitor can be either a peptide or not, it is not necessary to include this limitation in the claim.

The Examiner has also rejected claim 2 as it contains the negative limitation "inhibitor is not nuclear nucleolin." Applicants have amended the claim to more particularly define the invention, by referring to "cytoplasmic and cell surface expressed nucleolin." This limitation is supported in the specification in Example 12, page 119. Applicants have also deleted the objected-to term "able to" from claim 2.

Claim 3

The Examiner has also rejected claim 3 as indefinite for using the terms "peptide fragment," "pseudopeptide counterpart," and for having improper Markush language. Applicants have incorporated the limitations of claim 3 into claim 2 to more particularly define and describe the invention. Applicants have also amended this language to recite "peptidic fragment" instead of "peptide fragment" to make it more clear that the term refers to a fragment of an HIV receptor, wherein the fragment is a peptide.

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The Examiner also objects to the "pseudopeptide counterpart" phrase in claim 3. Specifically, the Examiner is concerned with the word "counterpart." While the *Callebaut* reference defines the term pseudopeptide, the Examiner alleges that it does not define the term counterpart. In considering our arguments regarding this term in the prior response, the Examiner states that homology between the peptide fragment and pseudopeptide counterpart is not a limitation of the claim. Applicants have amended claim 3 to recite that the pseudopeptide is homologous to the peptidic fragment. Applicants have also corrected the allegedly improper Markush language. Again, all of the limitations of claim 3 have been incorporated into claim 2 and amended for clarity.

Claim 4

The Examiner rejected claim 4 as indefinite for using the phrase "pseudopeptide which is homologous." The Examiner is concerned that the claim does not recite that the homology is sequence homology. Further, the Examiner is unclear as to how many amino acid sequence variations can be incorporated in a homologous structure. In other words, the Examiner has requested that Applicants define the degree of homology between the peptide and the homologous pseudopeptide.

Applicants have reviewed the specification and note that it discusses homology on page 16. Applicants note that the homologous peptides do not have decreased binding capacity and thus are equally able to alter and/or prevent the interaction between the receptor and the gp120 envelope glycoprotein. The homologous pseudopeptides can be evaluated using a ligand binding assay or ELISA assay. Thus, Applicants assert that this term is clear and that the person of ordinary skill in the art

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could easily make an assessment as to whether any given pseudopeptide was homologous.

Claim 6

The Examiner rejected claim 6 as indefinite for reciting improper Markush language. The Examiner also rejects claim 6 as indefinite for failing to recite the proper SEQ ID NO. The claim currently refers to SEQ ID NO: 1, but should refer to SEQ ID NO: 22. Applicants have amended the claim accordingly.

Therefore, Applicants request that the Examiner withdraw all of the definiteness rejections.

Anticipation and Obviousness Rejections

The Examiner has rejected claims 2-4, 6, 10, and 13 under 35 U.S.C. § 102 and 103 as anticipated by, or in the alternative, obvious over *Suzuki.* Applicants' last response argued that *Suzuki* disclosed nuclear nucleolin, while the present invention is directed to cytoplasmic and extracellular nucleolin. The Examiner believes that this difference is not adequately reflected in the claims. Applicants have amended claim 2 to incorporate the limitations of claim 3, and recite that if the inhibitor is a fragment of P95/nucleolin it is from cytoplasmic or extracellular nucleolin. Applicants, thus, request that the Examiner withdraw this rejection.

The Examiner also rejected claims 2-4, 6, 9-10, and 13 under 35 U.S.C. § 102 and 103 as anticipated by, or in the alternative, obvious over *Sapp. Sapp* also discloses

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nuclear nucleolin, while the present invention is directed to cytoplasmic and extracellular nucleolin. The Examiner believes this difference is not adequately reflected in the claims. As Applicants have amended claim 2 to recite that the fragment may be extracellular or cytoplasmic P95/nucleolin or a fragment thereof, Applicants request that the Examiner withdraw this rejection.

The Examiner further rejects claims 2-4, 6, 9-10, and 13 under 35 U.S.C. § 102 and 103 as anticipated by *Callebaut*. The Examiner alleges that *Callebaut* discloses the use of pseudopeptides for inhibiting HIV entry (infection) by interfering with the binding between gp120 and the cellular receptor.

Applicants have considered this reference in light of the Examiner's comments. *Callebaut* only discusses the TASP pseudopeptide. It does not teach or suggest the use of the peptidic fragment of extracellular or cytoplasmic P95/nucleolin, the peptidic fragment of P40/PHAPII, the peptidic fragment of P30/PHAPI, or pseudopeptides homologous to any of them. Applicants do not claim the TASP pseudopeptide taught by *Callebaut*. Applicants, thus, request that the Examiner withdraw this rejection.

Obviousness Rejections

The Examiner has rejected claims 2-6, 9-10 and 13 under 35 U.S.C. § 103(a) as obvious over *Srivastava*. *Srivastava*, like several of the other references, also discloses nuclear nucleolin, while the present invention is directed to cytoplasmic and extracellular nucleolin. The Examiner believes this difference is not adequately reflected in the claims. Applicants have, as discussed above, amended claim 2 to more particularly

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point out and define the invention, clarifying that only cytoplasmic and extracellular nucleolin, not nuclear nucleolin are part of the invention.

The Examiner rejected claims 2-4, 9-10, and 13 under 35 U.S.C. § 103(a) as obvious over *Rankin*. The Examiner states that *Rankin* discloses the full length cDNA sequence of nucleolin, but does not disclose specific peptides. The Examiner alleges that it would have been obvious for the Applicants to use the disclosed sequences to produce the polypeptides. Further, the Examiner states that the reference reads on all the rejected claims due to its open claim construction.

Applicants have considered the *Rankin* reference and it also teaches that nucleolin is a nucleolar specific protein that assists in processing of pre-ribosomal RNA as ribosomes are assembled. Thus, like the other references cited by the Examiner, *Rankin* does not teach or suggest cytoplasmic and extracellular nucleolin. Thus, Applicants amendment to claim 2 obviates this rejection as well.

Applicants request that the Examiner withdraw all of the obviousness rejections.

Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

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Respectfully submitted,

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Dated: October 7, 2002

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2. (Twice Amended) [~~A peptidic or non peptidic~~] An inhibitor molecule that [~~is able to alter and/or prevent~~] alters and/or prevents the interaction between a receptor located on the surface of an HIV infected cell and a gp120 envelope glycoprotein of said HIV, wherein the inhibitor is[~~not nuclear nucleolin~~] chosen from:

a) a peptidic fragment of extracellular or cytoplasmic P95/nucleolin,

b) a peptidic fragment of P40/PHAPII,

c) a peptidic fragment of P30/PHAPI,

d) a pseudopeptide homologous to a peptide fragment of extracellular or cytoplasmic P95/nucleolin,

e) a pseudopeptide homologous to a peptide fragment of P40/PHAPII, and

f) a pseudopeptide homologous to a peptide fragment of P30/PHAPI.

6. (Amended) The inhibitor molecule according to any one of claims 2 to 5, which comprises an amino acid [~~sequences selected from the following P95/nucleolin sequences~~] sequence chosen from:

- the sequence beginning at the amino acid in position 22 and ending at the amino acid in position 44 of SEQ ID NO: [~~1~~] 22;

- the sequence beginning at the amino acid in position 143 and ending at the amino acid in position 171 of SEQ ID NO: [~~1~~] 22;

- the sequence beginning at the amino acid in position 185 and ending at the amino acid in position 209 of SEQ ID NO: [~~1~~] 22; and

- the sequence beginning at the amino acid in position 234 and ending at the amino acid in position 271 of SEQ ID NO: [~~1~~] 22.

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13. (Twice Amended) A [~~therapeutic~~] composition comprising [~~a pharmaceutically effective amount of~~] an inhibitor molecule according to any one of claims 2, 4 to 6, or 9 to 10, [~~optionally~~] in combination with [~~another~~] at least a second compound, wherein the second compound is an anti-HIV molecule.

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